DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

November 23, 2001

TO: Arthur Lawrence, Ph.D.
Acting Principal Deputy Assistant Secretary for Health

FROM: Bernard A. Schwetz, D.V.M., Ph.D.,
Acting Principal Deputy Commissioner

SUBJECT: Rescheduling of BUPRENORPHINE from Schedule V to Schedule III of the Controlled Substances Act (CSA)

PURPOSE

Attached for your signature is a recommendation to the Drug Enforcement Administration (DEA) to reschedule buprenorphine from Schedule V to Schedule III of the Controlled Substances Act (CSA) and the scientific and medical evaluation that forms the basis for the recommendation as required by the CSA (21 U.S.C. 811 (b)).

BACKGROUND

The Food and Drug Administration has reviewed the abuse potential of several pending new drug applications for new dosage forms containing the partial opiate agonist, buprenorphine. Currently, the only product containing buprenorphine that has been approved by FDA is the original parenteral dosage form (Buprenex) that is presently controlled as a narcotic in Schedule V of the CSA. Buprenex is approved for the treatment of pain, whereas two of the pending buprenorphine NDAs, are for products that will be used in treatment of opiate addiction. These products are intended for use in office-based treatment of opiate addiction, as opposed to Narcotic Treatment Programs. The new office-based treatment approach is permitted for substitution treatment with narcotics that are in Schedules III, IV, or V of the CSA (21 U.S.C. 823(g)(2)).

With the approval of these pending new formulations, it is expected that availability of buprenorphine will increase in the United States as it has in other countries, and that diversion and abuse will follow. Thus, we have concluded that Schedule V provides an inadequate level of control to deal with the increased availability of the drug, its anticipated increased level of abuse, and the potential public health risks resulting from abuse of the new products. Following our review of new scientific, medical and epidemiological data, we have concluded that Schedule III is more appropriate for buprenorphine than Schedule V.

DISCUSSION

FDA's own experience with expansion in the availability of other opiate partial agonists or mixed agonist-antagonists in the United States is also predictive of increased buprenorphine abuse. This was seen, for example, after the analgesic butorphanol (Stadol NS) was approved as a nasal spray in late 1991 and marketed the following year. Stadol Injectable had been approved in 1978. From 1992 to 1994, most of the abuse reports for butorphanol were received. Ninety-seven percent of these reports were attributed to the new nasal formulation In contrast, only a small number of cases of abuse of the injectable product were reported during this time period.

The FDA present assessment relies on new evidence demonstrating that once buprenorphine availability expands from the original parenteral product to new dosage forms, buprenorphine use is likely to become more extensive. There is evidence that, with increased availability, individuals are taking buprenorphine in amounts sufficient to create a hazard to their health. In France, for example, since approval in 1996 of the high-dose sublingual formulation of buprenorphine, there have been over 100 new reports of death from buprenorphine abuse. Many of the decedents were not patients undergoing treatment for dependence or pain. Many of the same abuse problems as occurring in France and other countries are likely to occur in the United States when similar products become available unless further control measures are implemented. There appears in France to be significant diversion of the drug from legitimate drug channels, as reports indicate that diversion and forged prescriptions of buprenorphine tablets have been the source of buprenorphine abuse. Within the United States, people who are likely to experiment with buprenorphine for recreational purposes are believed to be particularly vulnerable.

FDA also has concluded based on the new data and reevaluation of earlier studies that dependence on buprenorphine is a major concern. Abuse of buprenorphine has been shown to result in a withdrawal syndrome of moderate intensity, a characteristic of Schedule III substances. Twenty percent of newborns to addicted mothers being treated with buprenorphine for opiate dependence have exhibited an abstinence syndrome severe enough to require medical intervention.

We have informed the National Institute on Drug Abuse (NIDA) of our scientific and medical evaluation and recommendation. The development of buprenorphine as a treatment for opiate addiction has been a major program of NIDA, which has provided assistance and encouragement to the pharmaceutical industry throughout the development. NIDA has had a prominent role in putting forth the concept of buprenorphine as the pharmaceutical agent appropriate for office-based treatment of opiate addiction in the United States, and has advocated its use in order to improve access to treatment by making treatment available to an expanded patient population. This Schedule III recommendation is consistent with that public health mission and will not impede office-based treatment of opiate addiction. Because of NIDA's prominent role in contributing to the development of buprenorphine for treatment of opiate addiction and

the potential appearance of a conflict-of-interest, the FDA assessment has been prepared without contributions from NIDA.

We have prepared the attached evaluation of buprenorphine, which is the basis for our recommendation.

B A Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.

Attachments (2):

Tab A - Recommendation to Reschedule Buprenorphine
Tab B- Letter from the DHHS to DEA

Buprenorphine
Recommendation to Reschedule Buprenorphine
From Schedule V to Schedule III of the Controlled Substances Act

I. RECOMMENDATION

The Food and Drug Administration (FDA) is recommending the rescheduling of buprenorphine from Schedule V to Schedule III of the Controlled Substances Act (CSA). Buprenorphine as a derivative of opium was originally a Schedule II narcotic. Buprenorphine was reclassified to Schedule V in 1984, following its 1982 approval as a parenteral analgesic. Several new buprenorphine products, in more accessible and potentially abusable dosage forms, are currently under development. FDA has evaluated recent data from abroad on the new dosage forms that relate to abuse, dependence, safety, and increased availability. After consideration of the scientific and medical evidence presented under the eight factors discussed below, FDA finds that buprenorphine meets the three criteria for placing a substance in Schedule III of the CSA under 21 U.S.C. 812(b).

The FDA assessment relies on new evidence demonstrating that expanded availability and use of the new dosage forms of buprenorphine is likely to increase abuse. Since approval of the high-dose sublingual formulation in France in 1996, over 100 reports of death linked to abuse of the new formulation have been received. Within the United States, people who are likely to experiment with an available drug for recreational purposes are particularly vulnerable.

FDA also has concluded based on the new data and reevaluation of earlier studies that dependence on buprenorphine is a major concern. An assessment of dependence is one of the three findings required to make a scheduling recommendation for a drug in Schedules II through V. Abuse of Schedule II substances may lead to severe psychological or physical dependence. For Schedule III substances, a finding of moderate or low physical dependence or high psychological dependence is required. For substances in Schedule IV, the required finding is abuse leading to limited physical or psychological dependence relative to substances in Schedule III. Finally, for substances in Schedule V, the required finding is that abuse may lead to limited physical or psychological dependence relative to Schedule IV substances (21 U.S.C. 812). Buprenorphine has been shown to produce a withdrawal syndrome of moderate intensity, therefore, as discussed in detail below, it meets the findings for Schedule III substances.

II. BACKGROUND

Pursuant to 21 U.S.C. 811(b), to recommend scheduling under the CSA, the Secretary of the Department of Health and Human Services is required to consider in a scientific and medical evaluation eight factors pertaining to control of a substance in the CSA and make three findings. The findings concern the relative abuse potential, legitimate medical use, and safety or relative dependence liability of a substance.

The FDA performs the administrative responsibilities for evaluating a substance for control under the CSA. The evaluation of buprenorphine, based on eight factors and the resulting three findings, are discussed in this document.

A. Status of Buprenorphine in the United States

As a derivative of opium, buprenorphine originally was a Schedule II narcotic. In 1982, FDA approved buprenorphine for relief of moderate to severe pain. Formulated for parenteral administration and marketed as Buprenex, the substance was rescheduled to Schedule V because its abuse potential was believed to be less than that of other pharmacologically similar opiates. Currently, buprenorphine has limited distribution in the United States, primarily to hospitals and clinics, because its sole availability is as a parenteral product.

FDA observed new and unanticipated public health problems when other opiates pharmacologically similar to buprenorphine were approved and marketed in non-parenteral dosage forms after having been on the market as parenterals. For example, butorphanol was responsible for significant public health problems after it was approved in a nasal spray formulation. The original parenteral formulation was approved 13 years earlier. After marketing of the new dosage form in 1992, the number of reports of abuse increased from an annual average of 5.4 (1978-1991) to 72 each year (January 1992-April 1994), a 130 percent annual increase. Another example is pentazocine which was first marketed in the 1970s and was also thought not to be abusable. Its easy accessibility and combined abuse with the antihistamine tripelennamine lead to the "T's and Blues" phenomenon, crushing and injecting the two tablets as a heroin substitute. Therefore, scheduling was necessary to alleviate this public health problem.

Abuse of transdermal opiates has also been observed. For example, excessive use of transdermal fentanyl (Schedule II), through multiple patch applications, chewing or other methods of altering the dosage form to increase absorption, or by extraction for injection of the active ingredient in a transdermal product, has been documented. Since large amounts of active ingredient often remain after use, the drug could easily be extracted for administration by injection or another route.

Several new buprenorphine products in more accessible dosage forms and larger doses are under development. These new products are likely to be abused to a greater extent and pose greater public health risks than the parenteral buprenorphine product that is currently available in the United States. Dramatic increases in abuse and diversion have been observed following approval and marketing of new formulations of older drugs due to changes in dose and formulation, as well as market expansion.

In other countries, abuse of buprenorphine tablet formulations has occurred by crushing them followed by intranasal or intravenous administration. Sublingual abuse of intact buprenorphine tablets has also been reported.

B. Status of Buprenorphine in Other Countries

Buprenorphine has been available in Europe and in other countries in a number of dosage forms since the late 1970s (Table 1). Low-dose sublingual and parenteral formulations are approved in numerous countries to treat pain. The high-dose sublingual dosage form has been available in France since 1996 and several other countries more recently for the treatment of opiate addiction. FDA is aware that other buprenorphine formulations may be under development.

FDA's decision to reschedule buprenorphine from Schedule V to Schedule III is based in part on the evidence gathered since 1996 from France and other countries documenting abuse of the sublingual formulations and fatal overdoses that have occurred with abuse of the high-dose sublingual formulations. The United States experience with the introduction of new formulations such as intranasal or transdermal systems is that the new formulations often result in increased availability and significant increases in abuse and dependence problems.

Table 1. Dates of Approval for Sublingual and Injectable Buprenorphine Products

COUNTRY	INDICATION: Moderate-to-Severe Pain		Opiate Dependence
	Injectable 0.3mg/mL	SL 0.1mg, 0.2mg, 0.4mg (low dose)	SL 2mg, 8mg (high dose)
Argentina	May 83		9 Dec 97
Australia	Aug 82	July 92	2 Nov 00
Austria	June 83	Oct 84	28 Jun 99
Bahrain		Mar 91	
Belgium	Mar 79	Apr 83	3 Nov 99*
Brazil	Mar 88	Mar 88	
Chile	Jan 90	Jan 90	
Colombia	June 82	Mar 84	
Costa Rica	Oct 89		
Czech Republic	July 84	Oct 84	Q1 2000
Denmark	Feb 80	Mar 82;Mar 90 (0.1mg, 0.4mg)	14 May 99
Dominican Republic	May 82		
Ecuador	Feb 86		
El Salvador	Apr 81		
Finland	May 81	Sep 82; Jan 92 (0.1mg, 0.4mg)	15 Feb 99
France	July 84	May 87	Sept 96
Germany	July 80	Dec 82	6 Jan 00
Guatemala	Nov 80		
Greece			3 Nov 99*
Honduras	Dec 80	Feb 91	
Hong Kong	May 87	May 87	7 April 00
Hungary	July 87	Feb 90	
Iceland	Aug 83		3 Aug 99
India	Mid-1980s	Mid-1980s	
Iraq	Mar 88	Mar 88	
Ireland	Feb 78	Jun 80	
Israel			Dec 00
Italy	Feb 82	Jun 84	2 Dec 99

Japan	May 83		
Luxembourg	Aug 81	Dec 81	8 July 98
Malaysia	Mar 87	Mar 87	June 01
Malta	Nov 80		
Mexico	Oct 89		
The Netherlands	June 81	Apr 89	
New Zealand	May 79	Apr 81; Jun 90 (Temgesic-NX)	
Nicaragua	Feb 81		
Norway	Apr 80	Mar 83; Feb 91 (0.4 mg)	17 Jan 99
Oman		Dec 85	
Pakistan	May 79	Oct 81	
Panama	Feb 80	Mar 83	
Peru	Aug 80		
Portugal	Aug 83	Aug 83	3 Nov 99*
Singapore	Jun 91	Jun 91	3 Feb 00
Slovak Rep			28 April 00
South Africa	Apr/May 84	Dec 89	
Spain	Oct 84	Nov 85	3 Nov 99*
Sri Lanka	Sep 81	Oct 84	
Sweden	Nov 81	Nov 86; Sep 90 (0.4mg)	8 Oct 99
Switzerland	Oct 79	Mar 83; Sep 91(0.4mg)	22 Dec 99
Syria			Feb 01
Thailand	Nov 80	Dec 82	
Turkey	Apr 86	Apr 86	Mar 00**
United Kingdom	Oct 77	Nov 80; Oct 90 (0.1mg, 0.4mg)	22 Dec 99
USA	June 85		
United Arab Emirates	Oct 83	Oct 83	
Venezuela	Sep 88	Sep 90	
Zaire	Mar 86	Mar 86	

*** Approved through mutual recognition through France; ** Scientifically approved but still awaiting pricing approval and finalization of local legislation on the management of addiction.**
NOTE: With the exception of the data from India, the information for the SL low dose (0.1, 0.2, 0.4mg) and the Injection was based on information in a table generated in May 1993 by Reckitt and Colman

Consistent with the requirements in 21 U.S.C. 811(b), FDA considers the factors pertaining to control of buprenorphine in the following discussion.

III. EVALUATION ACCORDING TO EIGHT FACTORS

Under 21 U.S.C. 811(c), eight factors pertaining to scheduling a drug are to be considered through a scientific and medical evaluation. The evaluation of buprenorphine with regard to those eight factors is presented here. In performing this evaluation, the FDA reviewed and analyzed an extensive body of literature and other data, including more than 200 articles from medical journals, numerous reports from the World Health Organization (WHO) and the United Nations International Narcotics Control Board (UN/INCB), and other relevant data. A detailed reference list is provided at the end of this document.

Factor 1: The drug's actual or relative potential for abuse

Evidence of actual abuse of the substance is indicative that a drug has a potential for abuse. The Agency has concluded that substantial evidence exists from experience abroad and in the United

States for the potential for buprenorphine abuse to significantly increase once other dosage forms become available in the United States.

When establishing evidence of the abuse potential of a substance, the following questions, discussed in the legislative history of the CSA, should be considered. [Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Congress Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603].

- **Is there evidence that individuals are taking the drug in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community?**

Abuse of buprenorphine sublingual tablets occurs in numerous countries, including France, New Zealand, Australia, United Kingdom, Spain, and India (see factors 4 and 5). Typically, in these countries, marketed buprenorphine sublingual tablets (which contain doses ranging from 0.1 mg to 8 mg) have been crushed, the buprenorphine active ingredient dissolved in aqueous medium, and injected to produce an opioid-like high or to prevent opioid withdrawal. Reports also document abuse of sublingual buprenorphine tablets through intranasal (snorting) and inhalation (smoking) routes. In France between 1996 and 2000, more than 100 deaths resulted from abuse of high dose buprenorphine intended for treatment of opiate withdrawal. Diversion is indicated as evidence shows that many of the decedents were not intended patients undergoing treatment for dependence or pain.

Although not yet available in the United States, once approved for marketing, other formulations such as sublingual and transdermal products, are likely to present many of the same abuse problems as the high-dose buprenorphine products currently marketed in France and several other countries. Accordingly, FDA believes that there is evidence that individuals will take buprenorphine in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community.

- **Is there significant diversion of the drug from legitimate drug channels?**

Reports indicate that diversion and forged prescriptions of buprenorphine tablets have been the source of buprenorphine abuse in several countries where the sublingual formulation is marketed. In several cases, national governments have responded by implementing stringent regulatory controls on buprenorphine to reduce abuse and diversion. (Farrell 1989, Dru 1999, Thirion et al., 1999, Arditti et al., 1992, Baumevieille et al., 1991, Lapeyre-Mestre et al., 1997, WHO 1988) Increased diversion and abuse has become an international concern. The United Nations International Narcotics Control Board (UN/INCB) publishes data on worldwide usage and availability of drugs regulated under the Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances. The published data help in assessing the impact of increased availability of the listed drugs. According to the UN/INCB, world manufacture of buprenorphine has increased substantially. Buprenorphine production has grown from 35 kg in 1980 to 460 kg in 1998. The United Kingdom has been the leading manufacturer. In 1994 and 1995, manufacture was relatively stable, at approximately 60 kg annually. Manufacture of

buprenorphine increased sharply in the United Kingdom to 274 kg in 1996, and 433 kg in 1998. Seven other countries have reported manufacture of buprenorphine since 1993, including India, Australia, China, the Czech Republic, Hungary, the Netherlands, and Poland. In France, a leading importer of buprenorphine, imports increased from 5 kg in 1994 to 159 kg in 1998. The increased availability coincides with an increase in buprenorphine abuse and reports of death. France is an appropriate comparator to the United States, because the drug is marketed there both for the treatment of pain and opiate dependence.

Thus far in the United States, the only source of buprenorphine has been the parenteral product (0.3 mg/mL). Currently, prescribing of the approved injectable buprenorphine product for treatment of pain is limited (annual usage data was only 0.6 kg in 1998 and projected use in 2001 is 1.0 kg). Diversion of this formulation has been negligible, primarily because it has had only limited distribution and availability. However, with the approval of new formulations, it is expected that availability will increase in the United States as it has in other countries, and that diversion and abuse will follow.

FDA's own experience with expansion in the use of other opiate partial agonists or mixed agonist-antagonists in the United States suggests the likelihood of increased abuse with buprenorphine, as seen, for example, after the analgesic butorphanol (Stadol NS) was approved as a nasal spray in December 1991 and marketed in 1992. From 1992 to 1994, there was a 600 percent increase in prescription sales for butorphanol. In contrast, there was no change in prescribing of Stadol Injectable from 1989 to 1994. By 1994, Stadol NS commanded 85 percent of total prescription sales and 96 percent of the retail market for all butorphanol products. In contrast, Stadol NS hospital prescribing was only 14 percent of the total. (See Table 2 below)

Table 2. Comparison of Prescribing of Butorphanol Products before and after approval of STADOL NS (December 1991). Source: IMS America, Inc.

YEAR	STADOL INJ	STADOL INJ	STADOL NS	STADOL NS
	Total Rx (000)	Retail Rx (000)	Total Rx (000)	Retail Rx (000)
1994	205	51	1162	1137
1993	222	53	787	767
1992	210	52	197	214
1991	222	69	N/A	N/A
1990	215	72	N/A	N/A
1989	223	64	N/A	N/A

An increase in reports of abuse paralleled increases in availability of the new product. Abuse increased to levels not seen following approval of the original butorphanol parenteral product in

1978. Between 1978 and 1994, 235 spontaneous reports related to abuse and dependence were submitted to FDA. Of the 235 reports, 165 (70 percent) were received between mid 1992 and 1994, coinciding with initial availability of the new formulation. Only 6 of the 165 reports received since mid 1992 were due to butorphanol injectable. In 1997, as a result of the increased rates of abuse and dependence, butorphanol was subsequently placed in Schedule IV of the CSA.

- **Are individuals taking the drug on their own initiative, rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs?**

Individuals who abuse opioid drugs and are addicted to opioids have used buprenorphine without the medical advice of a healthcare practitioner. Often these individuals are using buprenorphine as an opioid substitute, for its euphorigenic properties. (Lavelle et al., 1991, Rainey 1986, Strang 1985, 1991, Tracqui et al., 1998, Kintz 2000, Basu 1990, Bedi 1998, Robinson et al., 1993, Dore et al., 1997, Singh et al., 1992, Chowdhury et al., 190, 1998)

Opiate naïve individuals may also be using buprenorphine and may be obtaining the drug without medical authorization. Reports from those countries experiencing abuse show that access to the drug is being gained through falsified prescriptions, theft, and "doctor shopping" (Lavelle et al., 1991, Dore et al., 1997, Harper 1983, Lebedevs 1985, Quigley et al., 1984).

- **Is the drug a new drug that is so related in its action to a drug already listed as having a potential for abuse to make it likely that the drug will have the same potential for abuse as such drugs? Is it thus reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community?**

Buprenorphine is similar to other opioids in its euphoria and agonist effects. The pharmacology of buprenorphine contributes to both its efficacy in analgesia and in opioid substitution, as well as its abuse potential. It is classified as a partial agonist of the μ-opioid receptor because a plateau (or ceiling) for dose effects related to subjective and respiratory responses after acute administration has been described in the scientific literature (see also factor 2). Pure mu opiates like methadone and morphine continue to produce euphoria with increasing doses, unlike buprenorphine (Walsh et al. 1994, 1995). Buprenorphine, like hydromorphone, produced significant elevations of the Morphine-Benzedrine Group (MBG) of the Addiction Research Center Inventory (ARCI) and on the "good effects" visual analog scale (Bigelow and Preston, 1992). However, buprenorphine produces an increase in dysphoria at increasing doses, unlike hydrocodone which makes it less likely to be abused.

Buprenorphine has been shown to be effective in reducing or eliminating the withdrawal effects of opioid dependence and addiction. Withdrawal from buprenorphine is not as severe as withdrawal from Schedule II opioid agonists, such as methadone. The moderate opiate withdrawal syndrome of buprenorphine is attributable to its pharmacology as a partial agonist (see factor 2). A series of studies describes the buprenorphine withdrawal syndrome as moderate, which typifies drugs listed

in Schedule III (see factor 7). Additionally, higher doses of antagonists are needed to precipitate withdrawal from buprenorphine than are needed for the same response from full μ-opioid agonists. Amass et al. (1994) concluded, in addition, that discontinuation of buprenorphine can induce withdrawal symptoms sufficient to promote relapse to opioid use. Also, a significant neonatal withdrawal syndrome of moderate severity has been observed and documented (Fischer et al., 2000).

In addition to the new evidence gathered since introduction of buprenorphine for opiate dependence (France 1996) in the sublingual high-dose formulation, the FDA assessment is the result of the recent U.S. experience with the mixed opiate agonist-antagonist, butorphanol. When usage of butorphanol expanded from the injectable form following approval of a new, widely available and convenient intranasal formulation, abuse and diversion increased.

The increased availability after approval of new buprenorphine formulations is likely to lead to increased abuse, diversion, and public health concerns in the United States, as has been witnessed in other countries and as has been experienced in the United States after the intranasal butorphanol product was approved in December 1991.

Factor 2: Scientific evidence of its pharmacological effect, if known

Buprenorphine is a partial agonist at μ-opioid receptors and an antagonist at κ-opioid receptors. Buprenorphine displays a slow dissociation from the μ-opioid receptor. From animal and human studies, the analgesic potency of buprenorphine is 10 to 20 times greater than that of morphine.

If abused, buprenorphine dependence can result, though the buprenorphine withdrawal syndrome is of moderate severity (see factor 7). The scientific evidence of the pharmacology of buprenorphine is discussed below.

A. Preclinical Pharmacology

1. Receptor Selectivity

The concept of multiple opioid receptors has been proposed as the basis of opioid pharmacology. Activation of the μ-receptor involves production of supraspinal analgesia, respiratory depression, euphoria, reduced gastrointestinal motility, and physical dependence. Drugs with agonist activity at the κ-receptor induce spinal analgesia, miosis, and sedation and produce dysphoria and psychomimetic effects (disoriented and/or depersonalized feelings). The δ-receptor is also associated with analgesia, but its specific role is not clear.

Table 3. Narcotic Receptor Binding K_i (nM)

DRUGS	μ	δ	κ
Morphine	38	510	1,900
Nalbuphine	6.3	163	61
(±)-pentazocine	39	467	87
Butorphanol	1.7	13	7 4
Buprenorphine	0.77	2.2	1.1
Naloxone	1.2	19	12
Naltrexone	0.37	9.4	4.8

Source: Schmidt et al., 1985

Buprenorphine has been shown to have high affinities for opiate receptors relative to other substances. Table 3 shows inhibition constant values (K_is) for several opioids and for μ-, δ-, and κ- opioid receptors. K_is are used as a measure of the affinity of a drug for a receptor. Lower K_i values are indicative of a higher affinity for the receptor type being evaluated. K_is are relative values, and, under the same experimental conditions, may be used for comparison of affinity between drugs. The data also show that buprenorphine has similar affinity for the three opioid receptors (μ, δ, and κ) and stronger relative affinity for the μ-opioid receptor. Receptor binding studies do not allow differentiation between agonist and antagonist properties. These in vitro studies use guinea pig ileum and mouse vas deferens isolated organ assays.

Antinociceptive tests in living animals are generally used in initially characterizing the opioid profile of new drugs. Buprenorphine differs from both pentazocine and morphine in its difficult displacement by naloxone and by other opioids in receptor binding studies (Boas & Villiger 1985). Pentazocine is a weak μ antagonist and κ agonist. This combination of μ antagonism coupled with κ agonism is responsible for the designation of these drugs as mixed agonist/antagonist agents. An attenuated withdrawal syndrome correlates with the slow dissociation of buprenorphine from μ receptors.

2. Animal pharmacology

Buprenorphine is a potent, long-lasting, antinociceptive agent in animal models (Cowan et al., 1977a; Tyers et al. 1979, 1980, 1985; Shintani et al., 1982). The dose response curve for the opioid effects of buprenorphine in rodents is bell-shaped in a number of aspects, including respiratory depression (Rance, 1979). Buprenorphine lowers the heart rate in rodents, cats, and dogs; however, other hemodynamic variables are affected to less extent over a wide dosage range. The LD_{50}s for buprenorphine are higher than those of pentazocine, despite the 120- to 550- fold greater potency of buprenorphine as an analgesic (Cowan et al., 1977b).

Respiratory depression caused by buprenorphine and morphine in rats was comparable at low to moderate doses in rats and dogs. However, increasing doses produced a "ceiling effect" for buprenorphine that was not produced by morphine. Reduced and arterial

pCO2 increased in one dog at 0.1 mg/kg and in two other dogs at 1 mg/kg i.v. buprenorphine.

Another study compared the effects of buprenorphine and morphine on arterial pO2, pCO2, and pH in conscious rats. Buprenorphine (0.1 to 30 mg/kg, i.a.) produced a bell-shaped respiratory depressant curve. Buprenorphine produced alterations in pCO2 with doses as low as 0.1 mg/kg but increasing doses produced a "ceiling effect."

B. Clinical pharmacology

A number of buprenorphine clinical pharmacology and abuse liability studies have been carried out over the years. However, many of these studies only examine the subjective responses of single dose administration, and at high doses of a drug in opiate addicts, but do not examine the effects of repeated or multi-dose administration, or doses in the therapeutic range. Buprenorphine produced opioid agonist effects that were dose-related, with the suggestion of a "ceiling" of the agonist score between 8 mg and 16 mg of buprenorphine (Jasinski et al.,1978; Bigelow and Preston, 1992; Strain et al., 1999).

Weinhold et al. (1992) studied a group of nondependent opioid abusers. Various intramuscular buprenorphine doses, alone and in combination, were administered. In this population, buprenorphine (8 mg) was identified as an opioid 100 percent of the time, and the drug produced dose-related increases in subjective ratings. Consistent with other results in nondependent subjects, there was an increase in scores for "high" and "liking" on a subject-rated agonist scale. Ratings on the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) of the ARCI, a measure of sedation, also increased.

Walsh et al. (1994b, 1995b) compared the effects of a range of doses of buprenorphine and methadone. Buprenorphine produced significant dose effects on ratings of "high," "magnitude of high," "liking for the drug," and "good effects," without significant changes in ratings of "feeling sick" or "bad effects." The data suggested that there was a "ceiling effect" for a variety of the positive subjective responses beyond which there was no increase. The apparent ceiling in the population of experienced drug abusers varied from 16 mg for "high" or "any drug effect" down to 2 mg for "good effects" or "liking." Buprenorphine produced an increase in sedation that peaked at 4 mg and declined after 16 mg. Buprenorphine, however, did not produce changes in the euphoria scale, but did increase dysphoria which is likely to act as a deterrant to abuse. Overall positive effects of methadone increased linearly as the dose was raised, whereas those of buprenorphine were nonlinear and most effects reached a maximum at a dose ranging from 4 to 8 mg.

C. Bioavailability.

Buprenorphine is poorly bioavailable by the oral route, as a result of extensive metabolism in the small intestine and liver to its major metabolites: N-dealkyl buprenorphine (norbuprenorphine) and glucuronides of buprenorphine. Excretion of orally administered

buprenorphine is predominantly (70 percent) via the feces following biliary excretion of nonmetabolized drug and metabolites. The absolute bioavailability of sublingual tablets is approximately 30 percent when the extent of absorption of a sublingual solution is compared to an intravenous dose (Mendelson et al., 1997). Dissolving the sublingual buprenorphine tablet (8 mg) in aqueous alcohol enhances sublingual absorption: the bioavailability of the tablet is approximately 50 percent that of a sublingual aqueous alcoholic solution containing equivalent amounts of buprenorphine. (Nath et al., 1999; Schuh et al., 1999)

D. Absorption.

Following 4-mg, 8-mg, and 16-mg doses of sublingual buprenorphine, mean tablet disintegration times were 4, 6 to 7, and 7 to 8 minutes, respectively. Residual tablet fragments remain. Predose salivary pH ranged from pH 5.6 to 8.4. Postdose salivary pH ranged from 5.5 to 7.1. Dissolution studies showed that above pH 6, in vitro dissolution of buprenorphine from sublingual tablets was compromised, attributed to limited aqueous solubility. For a weak base like buprenorphine, only the nonionized form of the drug is absorbed across the oral mucosa. Absorption of lipophilic weak bases should increase with salivary pH increases. It appears that the high-lipid solubility of buprenorphine allows rapid absorption to the oral tissues. The tissue, however, serves as a reservoir that delays absorption to the systemic circulation.

E. Metabolism

Norbuprenorphine has a very long half-life and may accumulate to the same extent as parent drug during multiple dosing. Norbuprenorphine is a full μ-opioid agonist with low intrinsic activity and from animal studies has been shown not to readily enter the brain. Buprenorphine is extensively metabolized by the hepatic cytochrome P450 in humans, yielding norbuprenorphine (in vitro study). The specific form of P450 involved in the N-dealkylation is the P450 3A4 isoform. Buprenorphine and norbuprenorphine are also conjugated with glucuronic acid by a number of isoforms of UDP-glucuronosyl-transferases. At least two unidentified metabolites in urine account for less than 1 percent of the buprenorphine dose.

F. Drug Interactions

Full μ-opioid receptor agonists are known to produce respiratory depression, coma, and death if taken at high doses, especially by the intravenous route, and this is a common cause of fatality in heroin addicts.

Data show that most buprenorphine-related deaths have resulted from overdose and have been associated with drug combinations. The deaths involved abuse of buprenorphine and were similar to overdoses resulting from abuse of heroin. Deaths were often attributed to concomitant use of benzodiazepines, other sedative-hypnotics, and opioids. (Kintz 2000,

Tracqui et al., 1998)

The in vitro interaction between HIV-1 protease inhibitors and buprenorphine was investigated. The protease inhibitors are extensively metabolized by cytochrome P450 3A4. Methadone and buprenorphine, are each metabolized by CYP 3A4 as well. Potentially significant drug interactions of protease inhibitors co-administered with methadone or buprenorphine are likely. The resulting effect of these interactions is that the levels of each opiate may be significantly elevated.

Factor 3: The state of current scientific knowledge regarding the substance

Buprenorphine is a well-characterized synthetic opiate. Buprenorphine is manufactured from thebaine, a naturally occurring constituent of opium. For this reason, buprenorphine was originally classified as a Schedule II narcotic until 1984 when it was reclassified to Schedule V, following its 1982 approval as a parenteral analgesic. Chemically, the drug is 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol hydrochloride. CAS registry numbers are 53152-21-9 (hydrochloride salt) and 52485-79-7 (free base). Its molecular formula is $C_{29}H_{41}NO_4.HCl$, molecular weight is 504.11 (hydrochloride). The salt is a white crystalline powder that is sparingly soluble in water, but soluble in methanol or ethanol and practically insoluble in ether.

Factor 4: Its history and current pattern of abuse

As Table 1 shows, buprenorphine has gained worldwide approvals since the late 1970s, as an injectable product; the low-dose sublingual formulation (for treatment of moderate to severe pain) in most countries followed shortly thereafter. Approvals of the high-dose sublingual formulation (for treatment of opiate dependence) did not begin until the mid-1990s, with France being one of the first countries to approve the high-dose sublingual formulation in 1996. Argentina approved this formulation in late 1997; Luxembourg approved it in 1998; and the United Kingdom approved it in late 1999. Abuse involving the low-dose tablets has been reported since the 1980s. Increasing numbers of reports of buprenorphine abuse have been documented since 1996.

A. France

The recent experience in France provides considerable data about the use of buprenorphine for maintenance treatment of opiate addiction outside of the methadone clinic model. First marketed in France in 1987 as a low-dose sublingual analgesic (Arditti et al.), abuse and diversion were identified soon after approval. Between 1992 and 1993, buprenorphine was identified as the third most commonly appearing drug in falsified prescriptions in southwestern France (Baumevieille et al., 1997).

In December 1992, the French government instituted special dispensing and prescribing procedures, similar to those governing narcotic drugs.

- Buprenorphine was monitored by the French Medical Association.
- Prescriptions were required to be written on a voucher taken from a counterfoil prescription book that was specifically designed for narcotic drugs.
- Prescriptions could be filled by any pharmacy, but had to be retained by the pharmacist for three years.

In 1996, general practitioners were permitted to prescribe buprenorphine sublingual tablets for treating opiate dependence for up to 28 days per prescription, using the counterfoil prescription book. Doses prescribed were in the range of 4 to 16 mg/day. Auriacombe et al. reported that, when buprenorphine maintenance therapy was launched, the price of an 8-mg sublingual tablet was 100 francs. More recently, Dru (1999) reported that, in Paris at least, buprenorphine was easily accessible on the illicit market and was sold for 10 to 15 francs. The decrease in cost between the time buprenorphine maintenance was launched and 1999, is likely the result of the widespread availability of buprenorphine, by illegal and legal means. Because of continuing reports of abuse and diversion, on September 20, 1999, restrictions on dispensing of buprenorphine were tightened to a 7-day supply at one time per prescription.

B. United Kingdom (UK) and Ireland

Buprenorphine was approved in the United Kingdom as an injectable (1977) and a low-dose sublingual tablet (1980) for the treatment of pain (Table 1). Strang (1985) reported on the first appearance of buprenorphine abuse in the United Kingdom. Abuse was attributed to the use of stolen prescription forms. Sublingual buprenorphine tablets (0.2 mg), selling for 50 pence to 1 pound each, were frequently reported as being crushed, solubilized, and injected. Five tablets were considered to be the equal to the cost of heroin. In 1991, a new form of buprenorphine abuse was reported, again by Strang. Tablets (0.2-mg sublingual Temgesic) were crushed into a powder and snorted. A more rapid psychoactive effect was described. Recently, smoking (inhalation) of crushed tablets leading to pulmonary edema has been identified as a cause of death. As has been the experience in the United States, abuse and diversion of parenteral buprenorphine have not become public health problems in the United Kingdom. Data on marketing, usage, or abuse are unavailable on the high-dose sublingual buprenorphine tablets which were not approved for treatment of opiate dependence in the United Kingdom until late 1999.

In Scotland, abuse of buprenorphine combined with temazepam has been reported (Morrison, 1989, Sakol et al., 1989, Gray et al., 1989, Hammersley et al., 1990, Lavelle et al., 1991). One suggested explanation for increasing abuse of buprenorphine was a reported decrease in the quantity and quality of available street heroin (Sakol el al., 1989). A study by Gruer of drug use among 727 new clients in a needle-exchange program in Glasgow in 1992 showed that the most common injected drugs were heroin (61 percent) and buprenorphine (45 percent), and both of these drugs were frequently combined with a benzodiazepine. Opioid use in adolescents experimenting with buprenorphine was also documented by Coggans et al. (1991).

tablet) for the treatment of pain, "doctor shopping," forged prescriptions, pharmacy break-ins, and street availability were all reported to have increased for buprenorphine in 1986 and 1987.

C. Spain

In Spain, where the injectable and sublingual tablets have been available since the mid 1980s, addicts reported obtaining buprenorphine from drug dealers, and the most common method of use was to crush and inject the tablets after dilution. As in the United Kingdom, data on marketing, usage, or abuse are unavailable from Spain for the recently approved high-dose sublingual buprenorphine tablets.

D. India, Pakistan, Bangladesh, and Nepal

Buprenorphine abuse and diversion have become a significant problem throughout India and surrounding countries (Basu et al., 1990; Bedi et al., 1998; Chowdhury et. al, 1990; Singh et al., 1986, 1992; Kumar 1995). Government estimates of 50,000 buprenorphine abusers in Delhi alone account for 20 percent of opiate products abused in India since 1993 (Mudur 1999). The drug is sold often without valid prescriptions, illegally transported to neighboring countries, and sold for profit. Similar patterns of intravenous and polydrug abuse were reported from opiate clinics in other Asian countries. Primary buprenorphine abuse in treatment-seeking populations has also been documented in Pakistan (Niaz 1998) and Bangladesh (Chowdhury et al., 1998).

Of interest, data from Nepal show that two-thirds of first-time intravenous opiate abusers surveyed had initiated abuse with buprenorphine, as compared to 20 percent with heroin (Chatterjee et al., 1996). Findings such as these must be interpreted in the context of regional availability, relative costs and availability of heroin, as well as local issues including antinarcotic initiatives.

E. New Zealand

The New Zealand experience with abuse of a low-dose buprenorphine product is instructive. In March 1991, because of significant problems with intravenous abuse of crushed buprenorphine sublingual tablets, buprenorphine was reformulated by combining it with naloxone. The impact of this drug reformulation was evaluated by Robinson in surveys of new patients presenting for drug abuse treatment in Wellington, before (1990) and after (1991) the buprenorphine-naloxone combination product was introduced.

In 1990, prior to the reformulation, considerable intravenous misuse/abuse of the 0.2 mg tablets was reported. Eighty-one percent of the patients in Robinson's survey reported using buprenorphine tablets during the previous four weeks. It is noteworthy that although abuse declined, a considerable percentage of the patients (57%) reported misuse of the combination tablet in the 1991 survey done after the product was reformulated with naloxone.

Factor 5: The scope, duration, and significance of abuse

The pattern of abuse described in factor 4 appears to be typical of problems encountered elsewhere. In general, first indications of abuse are detected soon after introduction to the market of an easily accessible product, such as the sublingual tablet. In 1985 in Europe, the lack of dispensing restrictions and widespread use by heroin addicts and by individuals who were not already abusing heroin or other opiates resulted in the World Health Organization recommending buprenorphine for Schedule III of the Convention on Psychotropic Substances of 1971.

The sublingual dosage form, rather than the parenteral, is the product usually described as being abused. Abuse is accomplished by several routes, including manipulation of the dosage form (e.g., crushing, dissolving) and self-administration by originally unintended routes (e.g., inhalation, injection), all for the purpose of enhancing the drug's effects. Enhancement of absorption of the buprenorphine sublingual tablets can be accomplished by crushing the tablets, extracting the buprenorphine in alcohol, and sublingual administration of the alcoholic solution.

The factors likely to contribute to abuse of buprenorphine include the high cost, low quality, and low availability of heroin (Lavelle et al., 1991) versus the low cost, high availability, and pharmaceutical quality of buprenorphine. High availability results from "doctor shopping," prescription fraud, and pharmaceutical supply robbery. Other factors that contribute to abuse include the perception that buprenorphine is not a dangerous or addictive drug and the easy process of converting buprenorphine tablets into an injectable formulation.

As described above, a high incidence of buprenorphine abuse has been reported from France, New Zealand, Spain, Ireland, Scotland, and India. The drug abuse histories of the individuals abusing the drug appear to be relevant to the subjective response to buprenorphine. Identified at-risk populations are described in factor 6 (Public Health Risk). Surveys in several countries showed that buprenorphine, along with heroin, temazepam, and amphetamines, ranks among the top drugs most frequently abused (Lavelle et al., 1991, Arditti et al., 1992, Lapeyre-Mestre et al., 1997, Thirion et al., 1999, Shewan et al., 1998, Taylor et al., 1996, Coggans et al., 1991, Barnard et al., 1998). As already discussed, to reduce buprenorphine abuse, French authorities since 1992 have imposed progressively more narcotics restrictions on the prescribing and dispensing of buprenorphine drug products.

Deaths in France have been reported as related to the interactions of buprenorphine with other agents, including benzodiazepines, alcohol, and other opioids. Most of the deaths involved individuals who could not be identified as intended buprenorphine participants in a comprehensive treatment program nor as patients. Respiratory depressant effects are a major concern from buprenorphine overdose, as they are for other opiates.

Between January 1996 and May 2000, numerous deaths in France have been attributed to buprenorphine. The first 20 fatalities (Tracqui et al., 1998) were described in the open literature. An additional 117 fatalities, based on data from the Institute of Legal Medicine of Strasbourg and

13 other French forensic centers, have been recorded (Kintz 2000). Kintz considered the total number of buprenorphine-related fatalities in France to be an underestimation of the problem. Intravenous injection of crushed tablets, concomitant use of psychotropics, and the relatively high dosage of the buprenorphine formulation in France appear to be the major risk factors for such fatalities. All cases but one involved a concomitant intake of psychotropics. In the one case, cause of death was listed as tracheobronchial inhalation; blood buprenorphine concentration was 0.8 ng/ml. Benzodiazepines ranked first in association (present in 91 observations, of which 64 were nordiazepam). There were 37 cases involving neuroleptics, of which 26 were with cyamemazine. Eighteen cases (8 with tricyclics and 10 SSRIs) were with antidepressants. Concomitant use of other narcotics was observed: with morphine (12 cases), codeine (2 cases), methadone (4 cases), pethidine (1 case) and propoxyphene (4 cases). Four fatalities involved ethanol and buprenorphine.

A summary of postmarketing data from France indicates the use of buprenorphine among pregnant opiate-dependent women had resulted in 66 neonates experiencing some degree of withdrawal symptoms. Seven fetal deaths among mothers receiving sublingual buprenorphine tablets were reported in France. There is a need for large studies to compare buprenorphine with other opiates in opioid-dependent pregnant women (Fischer et al., 2000).

Factor 6: What, if any, risk there is to the public health

The opioid-like pharmacological profile of buprenorphine presents the same risks to the public health as other opioids. Respiratory depression resulting in death is a major risk of buprenorphine and other opioids, especially if overdosed or abused. In France, high-dose sublingual buprenorphine has been available by prescription since 1996 for the treatment of opiate dependence. During the first three years of marketing, approximately 50,000 individuals were treated for heroin addiction with the drug product. Many buprenorphine-related deaths have been reported in the published literature. The deaths involved individuals who were not in treatment for addiction, but who had obtained the drug through diversion or other unauthorized means. Most of the buprenorphine-related fatalities involved individuals who had taken other drugs or alcohol in combination with buprenorphine (Tracqui et al., Reynaud et al., Gaulier et al., and Cracowski).

Kintz (2000) reported details involving 117 fatalities, as described above (factor 5). Measurements of buprenorphine and norbuprenorphine levels in postmortem blood varied widely: 0.1 to 76.0 ng/mL and <0.1 to 65 ng/mL, respectively. All but one case involved concomitant intake of other psychotropics, which is typical of an opiate-addicted population. Benzodiazepines, present in 91 observations, were commonly associated with the buprenorphine deaths. Other cases involved neuroleptics, tricyclic antidepressants, SSRIs, alcohol, and other opiates. Tracheobronchial inhalation was frequently mentioned as the cause of death.

Relevant public health concerns relate to the identified at-risk populations, including neonates, recreational drug users (including youth), and experienced drug users.

A. Neonates

Neonatal abstinence syndrome (NAS) is the most common adverse event reported postmarketing in France for use of buprenorphine sublingual tablets by pregnant women. NAS is a typical opiate-like withdrawal syndrome, including tremor and autonomic hyperreflexia, that is mild to moderately severe in intensity. Between 1996 and the first six months of 1999, 66 reports of NAS were received by the manufacturer.

NAS has been reported for buprenorphine after childbirth or after weaning. In one study (Fischer et al., 2000), 20 percent of newborns to mothers in treatment with buprenorphine substitution for opiate dependence exhibited an abstinence syndrome severe enough to require treatment. Fischer et al. followed 15 pregnant opioid-dependent mothers until birth in an uncontrolled, open study. Most subjects (91 percent) had negative urine screens for other opioids. Mothers were maintained on buprenorphine for an average period of 11.7 weeks at a dose of 8.4 mg/day and decreased to 7.4 mg/day at delivery. NAS in the newborns was rated as moderately severe in 20 percent of the study population.

B. Recreational Drug Users

There is concern that young people who may be in the early stages of drug experimentation or who have been using opioid drugs in limited circumstances would be at risk and likely to try buprenorphine if it were available. In the 1980s, the .2 mg analgesic buprenorphine tablet was abused in Great Britain, primarily by young recreational drug users, some of whom were opioid naïve (Forsyth et al. 1993; Frischer 1992). Abuse by intravenous and intramuscular routes has also been documented.

C. Experienced Drug Users

Individuals who have had substantial drug abuse experience, have abused drugs for at least three years, or abused drugs intravenously comprise another identifiable at-risk population. Such individuals may have abused opioids without becoming physically dependent. The clinical pharmacology research on buprenorphine relating to abuse potential was conducted in nondependent subjects with past histories of opioid-experience (Jasinksi et al., 1978, 1989; Bedi et al., 1998; Walsh et al., 1994a). Opioid-experienced users reported positive drug effects and "liking" buprenorphine by various routes of administration (Bigelow and Preston 1992; Strain et al. 1999; Johnson et al. 2000). See Factor 2.

Examination of frequency of use data in Glasgow revealed that some opioid abusers used buprenorphine frequently. Buprenorphine was used as a heroin substitute at times when heroin was either unavailable, of low quality, or relatively too costly (Shewan et al. 1998).

Opioid-dependent individuals may use buprenorphine to help alleviate withdrawal symptoms. Robinson et al. reported that 63 percent of subjects from New Zealand used buprenorphine to lessen withdrawal effects, and 28 percent used the drug for euphoria.

Mendelson et al. (1996) evaluated the response of daily heroin users to buprenorphine (2-mg i.v.). Buprenorphine increased agonist subjective measures and decreased antagonist measures in this group. Part of the study design focused on potential street value for buprenorphine. Seven of eight subjects indicated that they would pay between $5 and $20 for the dose of buprenorphine received, which was somewhat less than what they were paying to support their habit. Four of the subjects reported they would pay this amount only to alleviate withdrawal.

Factor 7: The drug's psychic or physiological dependence liability

Dependence on buprenorphine following extended administration has been demonstrated using abrupt discontinuation or reduction of dosage and administration of an opioid antagonist. Both approaches produced symptoms of opioid withdrawal.

According to the *Diagnostic and Statistical Manual IV - Technical Revision* (2000), withdrawal is usually associated with substance dependence. Opioid withdrawal is characterized by a pattern of signs and symptoms that are opposite to the acute agonist effects of the opioid. Individuals in withdrawal have a craving to re-administer the agonist to reduce these symptoms. The first symptoms are subjective and consist of complaints of anxiety, restlessness, and muscle pains often in the back and legs, accompanied by a wish to obtain opioids (craving) and drug-seeking behavior, along with irritability and increased sensitivity to pain. In individuals dependent on short-acting opioids, such as heroin, withdrawal symptoms begin within 6 to 12 hours after the last dose. Symptoms take several days to emerge in the case of longer-acting drugs, such as buprenorphine. Acute withdrawal symptoms for a short-acting opioid usually peak within 1 to 3 days and gradually subside over 5 to 7 days. Less acute withdrawal symptoms can last for weeks to months. These more chronic symptoms include anxiety, dysphoria, anhedonia, insomnia, and drug craving. A physiological component is usually associated with withdrawal in cases of opioid dependence.

A low dose of naloxone administered to subjects chronically treated with buprenorphine did not precipitate abstinence (Jasinski et al., 1978). After abrupt withdrawal, however, the first withdrawal symptoms occurred on days 4 and 5 following discontinuation. The intensity of withdrawal was described as comparable to that seen with other substances, codeine (C-II) and dextropropoxyphene (C-II). Subjects (on days 14 to 15) requested and received morphine and diazepam to relieve the withdrawal symptoms. Kosten et al. (1990) studied the effect of opioid antagonists on buprenorphine-maintained patients; 2 to 3 mg buprenorphine was administered sublingually for 30 days. Oral naltrexone (1 mg) had no effect, but a high dose of naloxone (approximately 35-mg i.v.) precipitated significant withdrawal signs, though of less intensity than

that of methadone-maintained patients (36 mg/day) after receiving 1 mg of naltrexone. Similarly, Eissenberg et al., (1996) demonstrated that naloxone and naltrexone produced dose-related withdrawal and that higher doses of antagonists are required to produce withdrawal from buprenorphine observed in other studies that used full μ-opioid agonists. Significant precipitated abstinence was seen after 3 and 10 mg of intramuscular naloxone/70 kg and after 3 mg of oral naltrexone.

Seow et al., studied the withdrawal of heroin-dependent outpatients receiving 2 or 4 mg sublingual buprenorphine. After 21 days of controlled buprenorphine administration, the subjects were allowed to abruptly withdraw from buprenorphine. The subjects responded unfavorably to cessation of buprenorphine due to an increase in withdrawal symptoms. Subjects requested treatment of symptoms or transfer to a methadone program. These effects were reversed after re-administration of buprenorphine. In separate studies conducted by Kosten et al. (1988), San et al. (1992), and Fudula (1990), abrupt discontinuation of buprenorphine produced a withdrawal characterized as mild to moderately severe: effects peaked at 3 to 5 days, with a gradual lessening in intensity 8 to 10 days after the last dose.

Factor 8: Whether the substance is an immediate precursor of a substance already controlled

Buprenorphine is not an immediate precursor of a substance already controlled.

IV. FINDINGS AND RECOMMENDATION

After consideration of the scientific and medical evidence presented under the eight factors discussed above, FDA finds that buprenorphine meets the three criteria for placing a substance in Schedule III of the CSA under 21 U.S.C. 812(b). Specifically:

1. **Buprenorphine has a potential for abuse less than the drugs or other substances in Schedules I and II.**

Buprenorphine has high affinity for, and slow dissociation from, the μ-opioid receptor. In humans, buprenorphine produces a typical spectrum of opioid effects related to its partial μ-agonist activity, including euphoria, drug liking, pupillary constriction, respiratory depression and sedation. Reports of abuse of buprenorphine via the intravenous, sublingual, intranasal, and inhalation routes have been reported to occur in numerous countries where the drug has been available for treatment. In most case reports involving deaths related to buprenorphine, the drug was obtained by diversion and primarily abused in combination with other drugs (sedative-hypnotics, other opioids) and alcohol. However, in both preclinical and clinical studies, buprenorphine manifests a shallower dose response curve and "ceiling effect" for many actions compared to pure agonists such as morphine (C-II) and hydromorphone (C-II). Therefore, buprenorphine appears overall to have a potential for abuse less than the opiates in Schedule II, but greater than the mixed agonist-antagonists or partial agonists in Schedule IV.

2. **Buprenorphine has a currently accepted medical use in treatment in the United States.**

Buprenorphine is currently approved in the USA for medical treatment as an analgesic parenteral agent. Other dosage forms of buprenorphine are currently being developed.

3. **Abuse of buprenorphine may lead to moderate or low physical dependence or high psychological dependence.**

The withdrawal syndrome that develops after continued use is typical of opioids and is evidence of the capacity of buprenorphine to produce physical dependence. The intensity of the withdrawal syndrome has been evaluated clinically to vary from mild to moderately severe. Buprenorphine abuse and addiction among individuals not in treatment have been reported in countries where it is widely available, as evidenced by published reports in the public domain. Drug craving has been reported after discontinuing use of buprenorphine, which in some patients resulted in the need to resume use of heroin. This craving is indicative of psychophysiological dependence. Individuals dependent on buprenorphine can easily return to heroin use and vice versa. In addition, data show that buprenorphine is appealing as a drug of abuse in recreational drug users (including in youth). Finally, 20 percent of newborns to mothers in treatment with buprenorphine substitution for opiate dependence have exhibited an abstinence syndrome severe enough to require treatment.

FDA therefore recommends that buprenorphine be rescheduled from Schedule V to Schedule III.

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